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Ye.V. Stetsuk, V.I. Shepitko, N.V. Boruta, M.V. Rud, V.M. Sokolenko
Poltava State Medical University, Poltava

CHANGES IN THE CD68+ EXPRESSION OF THE INTERSTITIAL ENDOCRINE CELLS DURING CENTRAL BLOCKAGE OF THE HYPOTHALAMUS WITH TRIPTORELLIN AND THE ADDITION OF QUERCETIN IN RATS' TESTES

e-mail: Stetsuk78@gmail.com

The purpose of the study was to establish quantitative changes in the expression of CD68+ cells in the interstitial space and vessels of the testes under conditions of central blockade of luteinizing hormone synthesis by triptorelin with the addition of quercetin to the diet. The study was conducted on 35 sexually mature white male rats. The experimental group's animals were injected with a solution of triptorelin acetate at a rate of 0.3 mg of the active substance per kg of animal weight to simulate the central deprivation of the luteinizing hormone synthesis with the addition of quercetin. The central effect of blocking the synthesis of luteinizing hormone by triptorelin in the hypothalamus leads to an increasing increase in the distribution of the CD68 receptor in the interstitial space and in the vessels of the testis from the 30th to the 180th day of the experiment with a gradual decrease to the control indicators on the 365th day of observation. Adding the riboflavonoid quercetin to the diet significantly reduces oxidation processes and reduces triptorelin's negative impact on testicular tissue.

Key words: testes, interstitial endocrine cells, macrophages, M1, CD68+triptorelin, quercetin, fibrosis.

Є.В. Стецук, В.І. Шепітько, Н.В. Борута, М.В. Рудь, В.М. Соколенко

ЗМІНИ В ЕКСПРЕСІЇ CD68+ КЛІТИН ІНТЕРСТИЦІЙНОГО ПРОСТОРУ ЯЄЧКА ЩУРІВ ПРИ ЦЕНТРАЛЬНОМУ БЛОКУВАННІ ГІПОТАЛАМУСУ ТРИПТОРЕЛІНОМ ТА ДОДАВАННІ КВЕРЦИТИНУ

Дослідження було присвячено вивченню кількістних зміни в експресії CD68+ клітин в інтерстиціальному просторі та судинах сім'яників за умов центральної блокади синтезу лютеїнізуючого гормону трипторелін з додаванням в раціон харчування кверцитину. Дослідження проведене на 35 статевозрілих білих щурах-самцях. Тваринам експериментальної групи вводили розчин трипторелину ацетату із розрахунку 0,3 мг діючої речовини на кг ваги тварини для моделювання центральної деривації синтезу лютеїнізуючого гормону з додаванням кверцитину. Центральний вплив блокування гіпоталамусу синтезу лютеїнізуючого гормону трипторелін призводить до наростаючого збільшення розподілу рецептора CD68 в інтерстиціальному просторі та в судинах яєчка з 30-ї по 180-у добу експерименту, з поступовим зменшенням до показників контролю на 365-ту добу спостереження. Додавання в раціон харчування рібофлавоноїду кверцитину значно зменьшую процеси окислення і призводить до зменьшення негативного впливу трипторелін на тканини яєчка.

Ключові слова: сім'яники, інтерстиційні ендокриноцити, макрофаги, M1, CD68+ трипторелін, кверцитин, фіброз.

The study is a fragment of the research project "Experimental morphological study of cryopreserved placenta transplants action diphereline, ethanol and 1 % methacrylic acid on the morphofunctional status in a number of internal organs", state registration No. 0119U102925.

Infertility affects an average of 15–20 % of couples and is, therefore, a severe health problem. The incidence of male infertility is increasing due to various genetic, infectious and environmental factors. Patients with azoospermia are the most difficult to treat. Approximately 8 % of infertile men are diagnosed with either obstructive or non-obstructive azoospermia and often undergo (micro)surgical sperm extraction (testicular biopsy) and testicular sperm extraction. The obstruction is generally characterized by intact testicular parenchyma, preservation of sperm production in the seminiferous tubules, and normal morphology of the interstitial tissue. However, after a long period of obstruction, some macrophages can be detected in the seminiferous tubule epithelium [7].

Macrophages are present in all tissues of mammals, from mid-pregnancy throughout life, constituting a widely dispersed system in body organs. They contribute to homeostasis, responding to internal and external changes in the body. They act not only as phagocytes to protect against microbes but also to clean dead and aging cells, as well as through the functions of trophism, cell regulation, and cell repair. Based on this, macrophages can be considered a dispersed homeostatic organ [3]. Tissue macrophages are a distributed mononuclear phagocyte system contributing to the body's response to physiological changes in infectious conditions.

Mammalian testis have a significant population of macrophages located in the interstitial compartment. They have Fc and complement receptors, express macrophage-specific markers, produce interleukins, phagocytize and kill pathogenic organisms. These cells also contain trypan blue and plutonium, demonstrating acid phosphatase and nonspecific esterase activity [2]. Morphological studies of

rat testis revealed a specific ultrastructural combination of macrophages and interstitial endocrine cells. Namely, these cells project thin cytoplasmic processes to the deeply covered channels of macrophages. The electron-dense part of the macrophage membrane limits the channels. It can be hypothesized that these channels may be sites of intense exchange of molecules/signals between the two cell populations. In the normal adult testis, macrophages are found in the interstitium of the testis and are not found in any way in the seminiferous tubules. However, in the biopsies of infertile men, these cells (in addition to their interstitial location) can be seen in the lamina propria and epithelium of the seminiferous tubules and/or in the lumen of the tubules [8]. Interstitial endocrine cells are the main source of testosterone [9]. Still, they can also produce many non-steroidal factors, such as β-endorphin and prodynorphin, which are paracrine factors affecting macrophage function. Thus, the steroidal factors is adapted, regulated, and able to perform trophic [5] and protective functions locally and systemically compared to the nervous and endocrine systems. The expression of the CD68 receptor on the macrophage surface indicates that this cell is polarized according to the M1 phenotype [15].

Quercetin is a substance belonging to the group of plant pigments that adds color to many vegetables and fruits. Of all the flavonoids in the human diet, quercetin is the most abundant. Like other flavonoids, it is a powerful antioxidant, an inhibitor of leukotriene synthesis, a complex blocker of signal transmission and implementation in the calcium-mobilizing polyphosphoinositide system, and an activator of the adenylate cyclase cascade. These mechanisms are responsible for most of quercetin's pharmacological effects, some of which have been discovered recently and are currently being intensively studied. The above-mentioned pharmacological effects of quercetin are of great importance in treating inflammatory diseases, and they suggest the feasibility of including drugs based on it in the treatment regimens of patients in this group. Quercetin protects the body from the adverse effects of free radicals, such as damage to cell membranes, changes in DNA, and cell death. While protecting the body from damage caused by free radicals, the flavonoid can also help prevent several health problems, which we'll discuss now. At present, the scientific literature contains a limited amount of data on the relationship between the expression of the CD68 receptor on testicular macrophages and the activity of marker enzymes of macrophage polarization with longer-term blocking of the synthesis of luteinizing hormone in the experiment and the correction of this condition with quercetin.

The purpose of the study was to establish quantitative changes in the expression of CD68+ cells in the interstitial space and vessels of the testes under conditions of central blockade of luteinizing hormone synthesis by triptorelin with the addition of quercetin to the diet.

Materials and methods. The study was conducted on 35 sexually mature white male rats. Animals were randomly divided into 2 groups: control (10 animals) and experimental (25 animals). The experimental group's animals were injected with a solution of triptorelin acetate at a rate of 0.3 mg of the active substance per kg of animal weight to simulate the central deprivation of the luteinizing hormone synthesis [3]. Animals from the experimental group were sacrificed on the 30th, 90th, 180th, 270th and 365th days by overdose of ether.

Rats from the control group received saline injection. Experiment lasted for 365 days. Animals were kept in standard vivarium conditions at the Poltava State Medical University. Experimental animals were sacrificed in strict compliance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1986) and “General Ethical Principles of Animal Experiments” adopted by the First National Congress on Bioethics (Kyiv, 2001).

The study was approved and confirmed by the Bioethics Commission of the Poltava State Medical University *(*protocol No. 195 – 24.06.2021).

Using standard methods, the material was embedded in paraffin blocks, of which 4 μm sections were made and stained with hematoxylin and eosin [1]. Histological preparations were examined using Biorex 3 light microscope with a digital microfilter with software adapted for these studies (Serial No. 5604).

Immunohistochemical studies were conducted at the Department of Pathological Anatomy of Sumy State University. We used an immunohistochemical method using specific antibodies to visualise individual cellular components. Sections up to 5 μm were obtained from paraffin blocks made according to the abovementioned method, but without decalcification, and applied to highly adhesive SuperFrost slides (Thermo Scientific. USA). Glass slides with mounted sections were dried in a thermostat for 18 hours at 37 ºC. Then, they were deparaffinized and dehydrated in xylene and alcohols of increasing concentration. Receptors were unmasked in a citrate buffer medium (pH 6.0) in a water bath at 95–98°C. Primary antibodies were visualised using the UltraVision Quanto Detection System HRP Polymer

detection system (Thermo Scientific, USA). Amplification of the immunohistochemical reaction was carried out in a humid chamber with the help of Primary Antibody Amplifier Quanto (Thermo Scientific, USA) in dilutions recommended by the manufacturer using diaminobenzidine (Thermo Scientific, USA) as a dye. Hydrogen Peroxide Block and UltraVision Protein Block (Thermo Scientific, USA) were used to block endogenous peroxidase and non-specific background staining. After passing the immunohistochemical reaction with Mayer's hematoxylin, additional staining of the obtained preparations for better visualization was carried out. The study of cells of macrophage origin was carried out using monoclonal antibodies to the protein CD68 (KP6) in a dilution of 1:200 (Thermo Scientific, USA). CD68, a cluster of differentiation, is a 110-kD transmembrane glycoprotein highly expressed by human monocytes and tissue macrophages. Anti-CD68 antibody: Rabbit anti-Mouse, Rat CD68 Polyclonal Antibody. Catalog #MBS175328.

The results of immunohistochemical studies were evaluated by visual counting of the number of cells that reacted with the corresponding antibodies in the standard field of view. The quantitative level of cells of macrophage origin was determined using the CD68 receptor marker and was performed visually in the field of view.

The quantitative rate of CD68+ receptor proliferation in the interstitial space of the testes was calculated as follows: the number of cells on which the CD68+ receptor was detected and which were localized in the interstitial tissue and intravascularly was counted in 10 fields of view in each rat.

The obtained morphometric parameters were processed according to generally accepted rules of variational statistics. Microsoft Excel 2019 software based on the Windows 10 cooperative system was used. Results are presented as the mean trait value (M) and standard deviation (SD) for each sample or as a percentage increase over the control. The non-parametric Mann-Whitney test was used to determine the statistical significance of between-group differences, which was considered statistically significant at $P < 0.05$.

Results of the study and their discussion. When we calculated the testicular weight in experimental animals, the decrease in testicular volume was mainly due to the loss of the number of convoluted tubules from active spermatogenic cells and subsequent hypoplasia of the tubules, but it was also due to changes inside the testicular interstitium. We detected a small “type” of interstitial endocrine cells in large numbers in semi-thin sections from the 90th day, with a maximum on the 270th day of observation.

Immunohistochemical analysis of testicular tissue using the CD68 antibody in the experimental groups demonstrated a highly positive cytoplasmic response in macrophages in the testicular interstitial space (Figs. 1, 2, 3).

Macrophages were not predominant in type and number, accounting for 1:4 of the total number of cells in the interstitial space of the testis. In the early stages, interstitial endocrine cells predominated. Occasionally, we observed a weak positive reaction in the supporting cells of the convoluted seminiferous tubules in addition to macrophages. However, we did not count these cells in our analysis.

The highest cytoplasmic expression of cells with CD68+ was determined on the 30th to the 180th day in both experimental groups intravascularly and extravascularly.

The 30th day of observation was characterized by a statistical increase in cells with CD68+ compared to the control group of animals. When comparing the parameters of the two experimental groups, we established a stronger relationship between the indices in the experimental group with the addition of quercetin to the diet (2.11±0.12/3.27±0.33 and 3.03±0.47/4, 27±0.27) – the ratio is 0.645 and 0.709, respectively. This corresponds to a strong connection of the parameter by about 30 %.

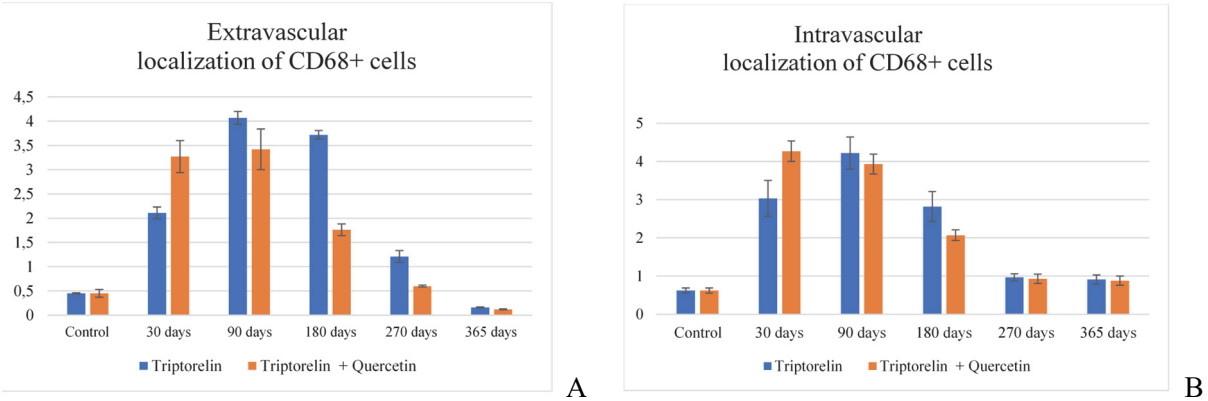

Fig. 1. Extravascular (A) and intravascular (B) localization of CD68+ cells

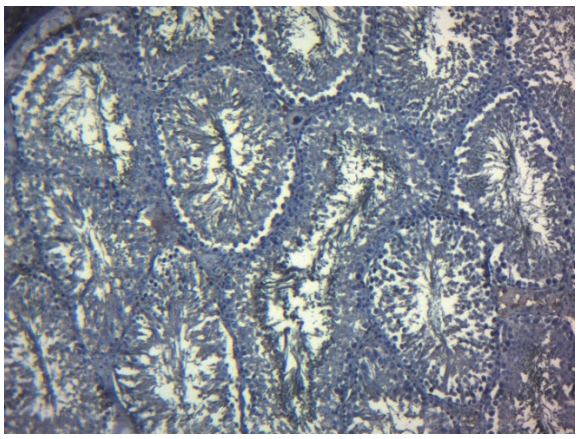

Fig. 2. Immunohistochemistry on testis tissue using antibodies against CD68+, with nuclear stain by Mayer's haematoxylin. Control group. x400.

Thus, when visually counting the population of intravascular CD68+ cells on the 90th day, it was 4.22±0.42 and 3.93±0.26 in the field of view, which was the most statistically reliable indicators in comparison with the control group and the previous term examination. This indicates a tension in the migratory activity of the pool of bone-marrow-type macrophages, which means a progressive activity of cytokines of the interstitial space of the testis in the group without quercetin.

The 180th day was characterized by increased values of the cell index, both in the vascular (2.82±0.39 and 2.07±0.14) and extravascular cell population (3.72±0.09 and 1.76±0.12), but with a downward trend.

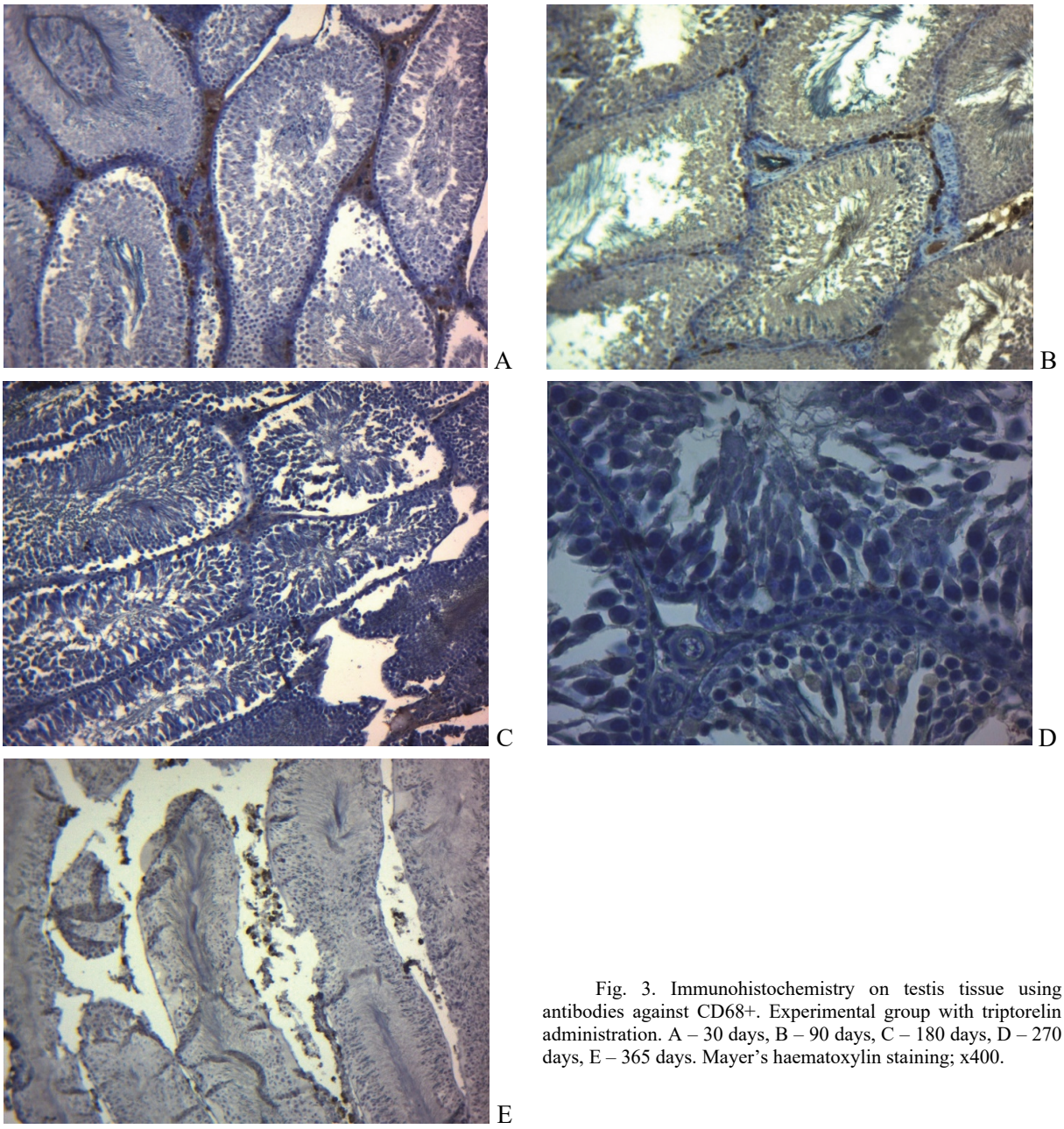

Fig. 3. Immunohistochemistry on testis tissue using antibodies against CD68+. Experimental group with triptorelin administration. A – 30 days, B – 90 days, C – 180 days, D – 270 days, E – 365 days. Mayer's haematoxylin staining; x400.

The 270th and 365th days of the experiment were characterized by a gradual decrease in both vascular and extravascular cell populations with CD68+ to the values of the previous periods of the experiment without a complete recovery to the state in the control group of animals.

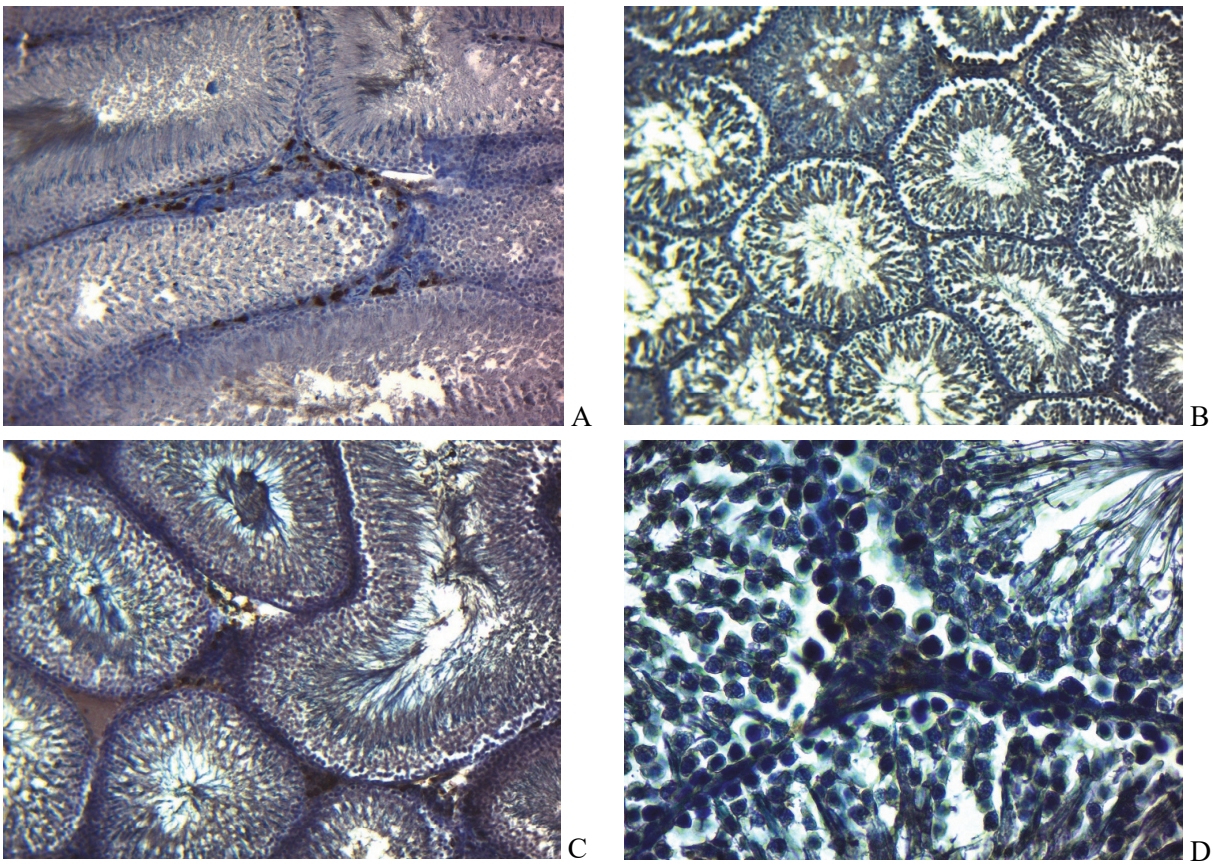

Fig. 4. Immunohistochemistry on testis tissue using antibodies against CD68+. Experimental group with triptorelin administration combined with quercetin. A – 30 days, B – 90 days, C – 180 days, D – 270 days. Mayer's haematoxylin staining; x400.

Several studies have shown that testicular macrophages play an essential role in regulating the steroidogenesis of interstitial endocrine cells and maintaining homeostasis inside the testis [10]. However, cases of orchitis demonstrate varying degrees of damage to the seminiferous tubules: hypospermatogenesis, impaired maturation of spermatogenic cells at the level of spermatids or spermatocytes, up to drastic pathological changes, such as "Sertoli cells only" syndrome – tubular fibrosis [13]. Our study noted increased CD68-positive cells in the testicular interstitium starting from the 30th day of observation. Stereological analysis showed a significant increase in the volume density of both CD68-positive and vacuolated endocrine cells and a positive correlation between the volume density of these cell types. It is known from literary sources that in histological sections of testicular biopsies with various pathologies, a combination of the above pathology can be recognized as "mixed atrophy" of the seminiferous tubules [11]. In obstructive orchitis, the interstitial endocrine cell structure and testosterone production are often altered compared to the controls. In biopsies of infertile men, interstitial endocrine cells are often hypertrophic and/or hyperplastic and diffusely located around hypoplastic seminiferous tubules [10]. An increase in these cells was detected in various forms of interstitial orchitis, including mixed atrophy [13]. A study by Bergh [13] showed that macrophages and interstitial endocrine cells similarly respond to unilateral cryptorchidism. In the cryptorchid testis, both macrophages and interstitial endocrine cells were reduced in size and number. Recent reports on the interaction between testicular macrophages and interstitial endocrine cells mainly refer to animal or in vitro models [13].

In addition, we wanted to draw a parallel between the expression of CD68 and the production of testosterone in the testicular tissue with the morphological characteristics of macrophages during the central blocking of the releasing factor of the hypothalamus with triptorelin. The results of our study, particularly its immunohistochemistry and morphometry, are in agreement with the results presented by Frungieri et al. [8], where increased numbers of CD68-positive cells were identified in the loose connective tissue of the interstitium and the lamina propria of hypoplastic seminiferous tubules, as well as in the seminiferous epithelium and tubule lumen. Based on these findings, it was suggested that testicular macrophages participate in regulating steroidogenesis both directly (through phagocytosis) and indirectly (through paracrine modulators). Increasing evidence shows that testicular macrophages are essential in regulating interstitial endocrine cell steroidogenesis and maintaining homeostasis within the testis. Under normal physiological and non-inflammatory conditions, macrophages play an essential role in developing interstitial endocrine cells. If macrophages are absent from the testicular interstitium, endocrine cells fail to develop normally. This suggests that macrophages provide essential factors for the growth and differentiation of interstitial endocrine cells. In infertile men with impaired spermatogenesis and/or chronic

orchitis, when macrophages are activated and secrete several inflammatory mediators, interstitial endocrine cell steroidogenesis is inhibited [11]. Our study indicated some changes in the interstitial tissue of the testis with an increased presence of positive CD68 cells. Stereological analysis emphasized the increased presence of CD68-positive cells in the early periods of observation, where the processes of oxidative stress in the testicular tissue prevail, and pro-inflammatory – M1.

The change in the polarization of testicular macrophages towards the predominance of a pro-inflammatory phenotype may be a decrease in the inhibitory effect of testosterone on testicular macrophages [9]. Another explanation for the shift in the polarization of testicular macrophages towards the dominance of the M1 phenotype may be the unmasking of sperm antigens due to the development of oxidative tissue damage, as described in our previous study [12]. An increased prevalence of CD68+ in the testes was observed on the 30th, 90th, and 180th days of the central blockade of luteinizing hormone synthesis with triptorelin.

Interestingly, on the 90th and 180th days, there is a significant predominance of intravascular expression of CD68+ over interstitial expression, which may indicate the active involvement of macrophages of bone marrow origin in the process in the testicles. This may be associated with an increased level of pro-inflammatory cytokines (IL-1, TNF-α, etc.) in the blood with a reduced level of testosterone production by interstitial endocrine cells [13]. Proinflammatory cytokines, in turn, stimulate the production of macrophages in the bone marrow and promote their migration to the site of cytokine production.

Quercetin is known to trap free radicals and can activate the body's antioxidant defence enzymes. It has an anti-inflammatory effect due to blocking the lipoxygenase pathway of arachidonic acid metabolism and decreasing the synthesis of leukotrienes, serotonin, and other inflammatory mediators [6].

In the study by P. Kumar et al. (2005) quercetin restored the concentration of many antioxidants (catalase, glutathione dismutase, superoxide dismutase) in the lungs of laboratory rodents infected with influenza A virus [14]. Given the acuteness of COVID-19 today, interest in quercetin as a means of preventing and treating it has resulted in a response from many specialists with scientific and medical profiles. In particular, in the protocol of (EVMS Medical Group) management of patients with COVID-19 to reduce the severity of the disease in particularly vulnerable persons (over 60 years of age). Such treatment reduced the risk of cell damage and inflammatory marker content [14]. The use of quercetin in our experimental study, as a natural riboflavanoid, is the protective effect of quercetin on the interstitial tissue of the testicles, thus changing the speed of the values of the indices in cells with CD68+ expression from the 30th to the 90th day of the experiment.

Conclusion

The central effect of blocking the synthesis of luteinizing hormone by triptorelin in the hypothalamus leads to an increasing increase in the distribution of the CD68 receptor in the interstitial space and in the vessels of the testis from the 30th to the 180th day of the experiment with a gradual decrease to the control indicators on the 365th day of observation. Adding the riboflavonoid quercetin to the diet significantly reduces oxidation processes and reduces triptorelin's negative impact on testicular tissue.

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D.O. Sukhomeylo, O.E. Reyzvikh[1], S.A. Shnaider[1], M.T. Khrystova, S.V. Kalynchuk[2], O.V. Maslov
Odesa National Medical University, Odesa
[1]State Establishment "The Institute of stomatology and maxilla-facial surgery National academy of medical sciences of Ukraine", Odesa, [2]Communal institution of higher education "Volyn Medical Institute" of the Volyn Regional Council, Lutsk

INFLUENCE OF THERAPEUTIC AND PROPHYLACTIC COMPLEX ON BIOCHEMICAL PARAMETERS OF RAT MUCOUS MEMBRANE OF GUMS UNDER MODELING OF EXPERIMENTAL CARIES

e-mail: sukhomeylod@gmail.com

The purpose of this study was to assess the effect of the proposed therapeutic and prophylactic complex on the biochemical parameters of the oral mucosa of rats under conditions of modeling experimental caries against the background of alimentary deficiency of vitamin D. Experimental studies were conducted on 42 one-month-old Wistar rats of both sexes, which were divided into 3 groups. Gingival homogenates were prepared and the level of biochemical markers of systemic inflammation was determined: elastase activity and malondialdehyde content, as well as urease activity, catalase activity and acid phosphatase activity. The therapeutic and prophylactic use of the proposed complex in rats helps to inhibit the detected disorders under conditions of experimental caries against the background of nutritional deficiency of vitamin D, normalizing the studied parameters to the level of intact animals, which indicates the expressed antioxidant, anti-inflammatory and antimicrobial properties of the complex.

Key words: experiment, caries, rats, vitamin D deficiency, biochemical indices.

Д.О. Сухомейло, О.Е. Рейзвіх, С.А. Шнайдер, М.Т. Христова, С.В. Калинчук, О.В. Маслов

ВПЛИВ ЛІКУВАЛЬНО-ПРОФІЛАКТИЧНОГО КОМПЛЕКСУ НА БІОХІМІЧНІ ПОКАЗНИКИ СЛИЗОВОЇ ОБОЛОНКИ ЯСЕН ЩУРІВ ПРИ МОДЕЛЮВАННІ ЕКСПЕРИМЕНТАЛЬНОГО КАРІЄСУ

Метою цієї роботи була оцінка впливу запропонованого лікувально-профілактичного комплексу на біохімічні показники слизової оболонки порожнини рота щурів в умовах моделювання експериментального карієсу на тлі аліментарного дефіциту вітаміну D. Експериментальні дослідження були проведені на 42 одномісячних щурах лінії Wistar обох полів, яких поділили на 3 групи. Готували гомогенати ясен та визначали рівень біохімічних маркерів системного запалення: активність еластази та вміст малонового діальдегіду, а також активність уреази, активність каталази і кислої фосфатази. Лікувально-профілактичне застосування у щурів запропонованого комплексу сприяє гальмуванню виявлених порушень за умов експериментального карієсу на тлі аліментарного дефіциту вітаміну D, нормалізуючи досліджувані показники до рівня інтактних тварин, що свідчить про виражені антиоксидантні, протизапальні та протимікробні властивості комплексу.

Ключові слова: експеримент, карієс, щури, дефіцит вітаміну D, біохімічні показники.

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Inadequate health status of children and adolescents is an actual problem of our time. The oral cavity plays an important role in the vital activity of the body, so the study of the state of its structural units in normal and pathological conditions occupies a prominent place in the research of scientists around the world [14, 15]. Pathological changes in the oral cavity in children require correct therapeutic and prophylactic intervention, a prerequisite for the effectiveness of which is a deep knowledge of the relevant etiopathogenetic mechanisms. There are both independent and symptomatic causes and factors that determine the development of dental pathology. For many years, the physiological role of vitamins